✓Volume of distribution: Drugs with a small volume of distribution (less than 1 L/kg) available in central circulation for removal. Large volumes of distribution cannot be removed (digoxin and tricyclic antidepressants), even if the protein binding is very low.

2) *Procedure-related factors affecting drug removal*

✓Type of dialyzer: High flux, widely used now

✓Blood flow rate: Elevated rates increase delivery and maintain gradient across membrane.

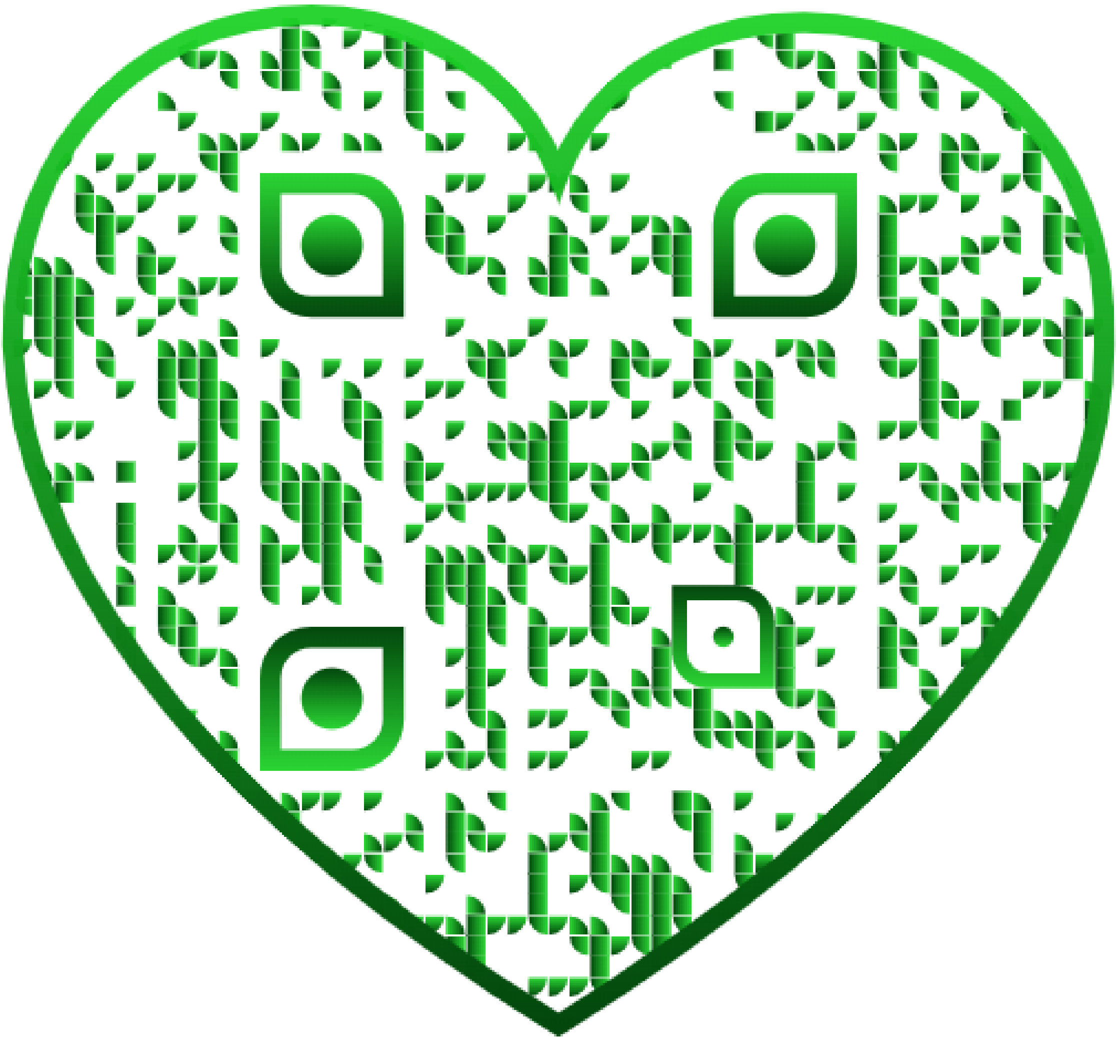
✓Duration of dialysis session

✓Dialysate flow rate. High rates of flow increase removal by maintaining the gradient across membranes.

REVIEW QUESTIONS

1. One of the following statements is **not true** about acute kidney injury
   A. NSAIDs cause prerenal AKI through vasodilation of afferent arterioles
   B. Furosemide is the diuretic of choice in the management of AKI
   C. Majorly, AKI is reversible
   D. The most prevalent type of AKI is the prerenal AKI
2. A patient with GFR of 12 mL/min/1.73 m^2:
   A. Has normal renal function
   B. Has kidney damage but normal GFR
   C. Has end stage kidney failure
   D. None of the above
3. Regarding the etiologies of chronic kidney disease:
   A. Advanced age and reduced kidney mass are progression factors
   B. The majority of CKD from diabetes is among type 1 DM.
   C. Initiation factors like DM are modifiable pharmacologically
   D. Susceptibility factors are proven to directly cause CKD
4. BUN: serum creatinine is elevated in:
   A. Prerenal AKI B. Intrinsic AKI
   C. Post renal AKI D. Obstructive AKI
5. For patients with chronic renal failure reduction of proteinuria is possible with:
   A. Insulin B. Diuretics C. Statins D. ACEi

Questions 6–8 pertain to the following case. Mr. BB, A 48-year-old man (weight 70 kg), is admitted to the intensive care unit after an acute myocardial infarction. He has a history of type 2 diabetes, hypertension, and tobacco use. Current medications include metformin 500 mg orally twice daily, lisinopril 20 mg/day, nicotine patch 14 mg/day applied each morning, and aspirin 81 mg/daily. Before admission, his kidney function was normal (SCr 1.0 mg/dL); however, during the past 24 hours, his kidney function has declined (BUN 20 mg/dL, SCr 2.1



mg/dL), despite receiving 3 L of intravenous fluids. His urine shows muddy casts. Urinary volume has been 300 mL over the past 12 hours. His current blood pressure is 110/70 mm Hg. He has edema and pulmonary congestion.

6. Which is the most likely cause of this patient's impaired kidney function?
   A. Prerenal azotemia
   B. Intrinsic renal disease
   C. Postrenal obstruction
   D. Functional AKI
7. Which medication is best to discontinue at this time because of its potential adverse effect on kidney function?
   A. Lisinopril
   B. Nicotine patch.
   C. Metformin
   D. Aspirin
8. Which intervention is most appropriate to add at this time?
   A. Intravenous NS.
   B. Hydrochlorothiazide.
   C. Furosemide.
   D. Fluid restriction
9. The glomerulus is primarily responsible for _______ of unbound drug in the kidney:
   A. Filtration
   B. Reabsorption
   C. Secretion
   D. Endocytosis
10. J.S. is a 70-year-old male (173 cm, 85 kg) with a history of hypertension and CKD. His serum creatinine today is 1.50 mg/dL. What is his estimated creatinine clearance?
    A. 55.0 mL/min
    B. 43.5 mL/min
    C. 37.2 mL/min
    D. 29.4 mL/min
11. An 81-year-old male long-term care geriatric patient is admitted to the hospital with altered mental status. His admission laboratory values show a BUN of 43 mg/dL and serum creatinine (S_{cr}) of 2.8 mg/dL. Urinalysis reveals presence of white blood cells, red blood cells, and granular casts. His calculated fractional excretion of sodium (FE_{Na}) is 2.2%. The most likely etiology of AKI is:
    A. Intrinsic AKI
    B. Bladder obstruction
    C. Postrenal AKI
    D. Functional AKI
12. Which of the following strategies can be used to overcome diuretic resistance in a fluid-overloaded patient who is poorly responding to bolus doses of furosemide?
    A. Change furosemide to bumetanide
    B. Add bumetanide
    C. Change furosemide to a continuous infusion
    D. Change furosemide to hydrochlorothiazide
13. A 36-year-old man is diagnosed with intrinsic AKI secondary to a prolonged exposure to intravenous tobramycin. Which of the following pathophysiologic processes has most likely occurred in this case?
    A. Glomerular damage secondary to severe inflammation
    B. Drug hypersensitivity reaction leading to interstitial inflammation
    C. Bladder outlet obstruction
    D. Tubular epithelial cell damage

14. Which of the following medications is most likely to cause of acute tubular necrosis in a 75-year-old hospitalized patient?
A. N-acetylcysteine
B. Acyclovir
C. Dopamine
D. Contrast dye
15. Hypertensive patients with CKD should limit dietary sodium to less than:
A. 1 g/day B. 1.5 g/day C. 2 g/day D. 2.5 g/day
16. A 28-year-old female patient with diabetic CKD and albuminuria on an angiotensin-converting enzyme inhibitor (ACEI) becomes pregnant. The ACEI is discontinued. Which of the following drugs has been shown to reduce albuminuria and is safe for use in pregnancy?
A. Verapamil
B. MetoproloL
C. Spironolactone
D. Candesartan
17. Which of the following may appear in patients with nephritic syndrome but not nephrotic syndrome?
A. Proteinuria
B. Edema
C. hypercoagulable state
D. Hematuria
18. Patients with nephrotic syndrome are commonly advised to:
A. Restrict sodium intake
B. Restrict protein intake
C. Consume a low-fat diet
D. All of the above
19. Which of the following parameters is useful to predicting the risk for renal function deterioration in patients with glomerulonephritis?
A. Edema
B. Proteinuria
C. Coagulopathy
D. All of the above
20. Use of statins in patients with glomerulonephritis may:
A. reduce VLDL and LDL cholesterol levels
B. reduce risk for cardiovascular disease
C. reduce the proteinuria progression
D. all of the above
21. Which of the following agents is/are often used as first-line therapy for inducing remission in patients with recently diagnosed minimal-change nephropathy?
A. Steroid
B. Steroid and cyclosporine
C. Steroid and azathioprine
D. Steroid and cyclophosphamide

Questions 22 and 23 pertain to the following case.

A.M. is a 54-year-old man who presents with diagnosed type 2 DM. His serum creatinine (SCr) concentration is 1.6 mg/dL, and a spot albumin/creatinine ratio (ACR) is 410 mg/g. His blood pressure is 145/89 mm Hg and hemoglobin A1C (A1C) is 7.1%.

22. Which would provide the best therapeutic intervention at this time to slow A.M.'s diabetic kidney disease progression?
A. Clonidine.
B. Lisinopril.
C. Metoprolol.
D. Amlodipine.

23. Which dietary intervention is best to reduce A.M.'s albuminuria?
    A. Protein-restricted diet.
    B. Omega-3 fatty acid administration.
    C. Low-carbohydrate (Atkins) diet.
    D. Low-potassium diet.

Questions 24 and 25 pertain to the following case.

A 62-year-old man presents with a history of hypertension and newly diagnosed type 2 diabetes (DM). He reports occasional alcohol use and smokes I pack of cigarettes/day. His medications include HCT and valsartan. His current blood pressure is 130/80 mm Hg. A spot urine dipstick shows ACR 350 mg/g. A recent SCr is 2.3 mg/Dl (SCr was 2.4 mg/dL 6 months ago). His eGFR is 29 mL/minute/1.73 m2.

24. Which category best classifies this patient's GFR?
    A. Stage G3a. B. Stage G3b.
    C. Stage G4. D. Stage G5.
25. Which best represents this patient's albuminuria category?
    A. A1 B. A2.
    C. A3. D. A4.
26. A 72-year-old woman (height 63 inches, weight 48 kg; ideal body weight 52.4 kg) presents to the clinic. She is visibly small and frail. Her SCr, unchanged from the past year, is 0.4 mg/dL. Which is the best method to assess kidney function in this patient?
    A. Cockcroft-Gault.
    B. Modification of Diet in Renal Disease (MDRD).
    C. CKD-EPI.
    D. 24-hour urine collection for CrCl.
27. A 60-year-old man presents with a medical history of hypertension and newly diagnosed type 2 DM at the clinic. He reports neither alcohol consumption nor smoking. His only medication is atenolol 25 mg daily. His current blood pressure is 155/96 mm Hg and heart rate is 76 beats/minute. His ACR is 350 mg/g. A recent SCr is 1.9 mg/dL. His eGFR is 37 mL/minute/1.73 m^2. Enalapril is added to this patient's regimen. Two weeks later, he presentsback to his physician. His blood pressure is 145/93 mm Hg. A repeated SCr measurement is 2.3 mg/dL, and his serum potassium is 5.2 mEq/L. Which is the best recommendation for this patient?
    A. Change enalapril to diltiazem. Monitor blood pressure, SCr, and potassium concentration in 2 weeks.
    B. Add chlorthalidone 12.5 mg daily. Monitor blood pressure, SCr, and potassium concentration in 2 weeks.
    C. Change enalapril to valsartan.
    D. Increase atenolol.

CHAPTER 4: CARDIOVASCULAR DISORDERS

4.1. Hypertension

✍ **Definition**: *Hypertension* is defined as persistently elevated arterial blood pressure (BP); (1) having an SBP of 140 mm Hg or greater; (2) having a DBP of 90 mm Hg or greater. Starting at a blood pressure of 115/75 mm Hg, every increase of 20 mm Hg in SBP and/or increase of 10 mm Hg in DBP is associated with a doubling of the risk of death from stroke, heart disease, or other vascular disease.

Table 4.1 Blood pressure classification[1]

BP Classification	SBP (mm Hg)	VS	DBP (mm Hg)
Normal	<120	AND	<80
Elevated	120-129	AND	<80
Hypertension			
Stage 1	130-139	OR	80-89
Stage 2	≥140	OR	≥90

Key Concepts *Individuals with SBP and DBP in 2 categories should be designated to the higher BP category*

✍ **Prevalence**

- Hypertension is the major modifiable risk factor for CV disease and stroke. There are 1.13 billion of the global population in 2019 with a global prevalence of 22%[2].
- Prevalence depends on: **race** (blacks > whites), **age**: 50% among those 60-69 year, 75% in >70 years, **gender**: less in younger women. F:M= 0.6 at 30 yr but 1.1-1.2 at 65 years
- According to a systematic review and meta-analysis in Ethiopia, the pooled prevalence of hypertension was 21.8% with the highest being in Addis Ababa

---

[1] Carey RM, Whelton PK: **Prevention, detection, evaluation, and management of high blood pressure in adults: synopsis of the 2017 American College of Cardiology/American Heart Association Hypertension Guideline.** *Annals of internal medicine* 2018, **168**(5):351-358.

[2] WHO. **Hypertension fact sheets** 2021.

(25.4%)[1]. But the cut-off point for this figure is the previous hypertesion diagnosis criteria (≥140/90 mmHg) which may underestimate the prevalence of hypertesive patients.

- HTN is adequately controlled in only 52.5% of patients with HTN.

BP measurement

- Periodic screening for all people older than 21 years is recommended.
- **Step 1: Obtain an appropriate home BP measurement device.** Choose a fully automated device (avoid auscultatory home devices). Choose an arm device (brachial BP). Use wrist monitors only for patients whose arm circumference prevents proper fitting. Choose validated devices, if possible. Ensure correct cuff size.
- **Step 2: Prepare for BP measurement.** Empty bladder; refrain from drinking caffeine or smoking 30 min before measurement; rest at least 5 min before BP measurement; sit with back supported and feet flat on the floor (legs uncrossed); place cuff directly above the antecubital fossa.
- **Step 3: Measure BP**. Take two readings 2 min apart. Avoid unnecessary movement or talking during measurement. Minimize excessive measurements.
- **Step 4: Record BP values** with date and time, noting anything unusual (e.g., pain, stress, illness, missed medication).

Etiology

a) Essential HTN: 90% (no identifiable cause)
b) Secondary HTN: Primary aldosteronism, renal parenchymal disease, thyroid or parathyroid disease, medications (cyclosporine, NSAIDs, sympathomimetics), pheochromocytoma

Diagnosis

a) Periodic screening for all people older than 21 years
b) Patient should be seated quietly in chair for at least 5 minutes.
c) Use appropriate cuff size (bladder length at least 80% the circumference of the arm).
d) Take BP at least twice, separated by at least 2 minutes.
e) The average BP on two separate visits is required to diagnose HTN accurately

Pathophysiology

- ***Blood pressure*** is the function of *peripheral vascular resistance* and *cardiac output* (BP = PVR × CO) and cardiac output is the function of heart rate and stroke volume (CO = HR × SV)
- ***Peripheral Vascular Resistance***
- ***Increased Cardiac Output***

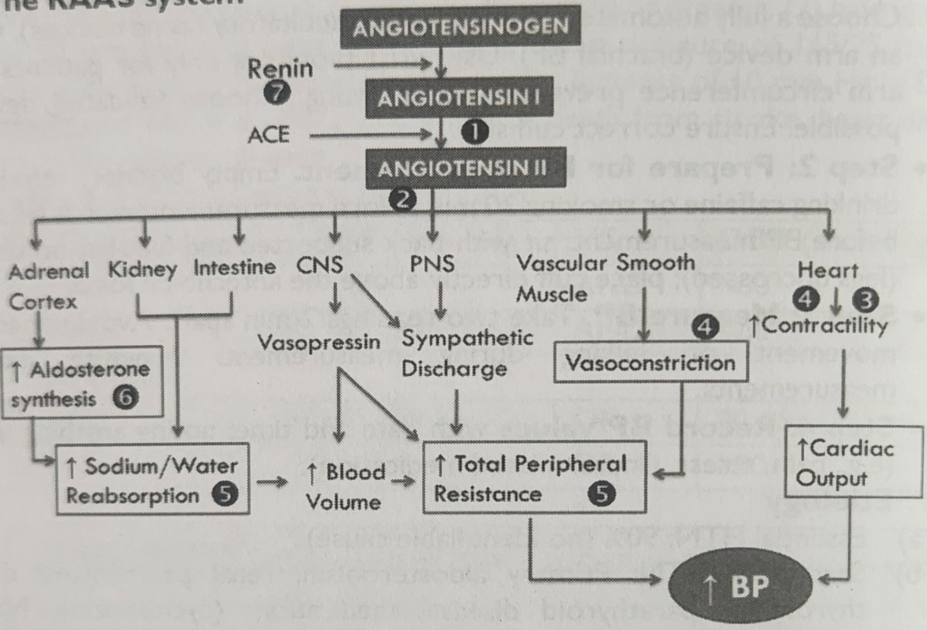
---

[1] Tiruneh SA, Bukayaw YA, Yigizaw ST, Angaw DA: **Prevalence of hypertension and its determinants in Ethiopia: A systematic review and meta-analysis.** *Plos one* 2020, **15**(12):e0244642.

- ✓ Excess stimulation of the RAAS
- ✓ SNS over activity
- ✓ Genetic alterations of cell membranes
- ✓ Endothelial-derived factors
  - ✓ Hyperinsulinemia resulting from obesity or the metabolic syndrome

- ✓ Increased intravascular volume from excess Na intake
- ✓ Increased intravascular volume from renal Na retention
- ✓ Excess stimulation of the RAAS
- ✓ SNS over activity

- **The RAAS system**


ANGIOTENSINOGEN
Renin
❼
ANGIOTENSIN I
ACE
❶
ANGIOTENSIN II
❷
Adrenal Cortex
Kidney
Intestine
CNS
PNS
Vascular Smooth Muscle
Heart
❹ ❸
❹
↑Contractility
Vasopressin
Sympathetic Discharge
Vasoconstriction
↑ Aldosterone synthesis ❻
↑ Sodium/Water Reabsorption ❺
↑ Blood Volume
↑ Total Peripheral Resistance ❺
↑Cardiac Output
↑ BP

❶ ACEIs, ❷ ARBs, ❸ BBs, ❹ CCBs, ❺ Diuretics, ❻ Aldosterone Antagonists, ❼ Direct Renin Inhibitors: aliskiren

Figure 4.1 Regulation of BP by RAAS system

✍ Effects of Hypertension (Target organ damage)

- HTN is a risk factor for atherosclerosis. Accelerated atherogenesis in hypertension is accompanied by proliferation of smooth muscle cells, lipid infiltration into the vascular endothelium, and an enhancement of vascular calcium accumulation. It results in injury to major organs – **target organ damage.** The **heart**, the **CNS**, and the **kidneys** are major target organs. Target organ damage can be acute or chronic.
- **Effects on the Heart**: HTN → hypertensive heart diseases a result of:
  - ✓ Increased afterload
  - ✓ Coronary atherosclerosis
  - ✓ Most deaths in HTN are cardiac (from CHF or AMI).
- **Effects on the CNS**
  - ✓ Retinopathy

- ✓ Cerebral infraction/ischemia: due to atherosclerosis of cerebral arteries: TIA and ischemic stroke
- ✓ Cerebral Hemorrhages: due to elevation of ABP and development of microaneurysms.
- ✓ Hypertensive encephalopathy

- **Effects on kidney**
  - ✓ Glomerular atherosclerosis of the afferent and efferent arterioles and the glomerular capillary tufts → CKD.
  - ✓ The mechanism is hypertensive nephrosclerosis which manifests as proteinuria + microscopic hematuria.

✍ Treatment

- *Benefits of treating elevated BP*
  - a) Decreased risk of stroke (by 35-40%)
  - b) Decreased risk of MI (by 20-25%)
  - c) Decreased risk of HF (by 50%)
- ***Desired Outcomes**: Goal BP for Chronic Treatment*[1]
  - ✓ Most patients including patients with clinical ASCVD (secondary prevention), diabetes, or CKD; primary prevention patients regardless of 10-year ASCVD risk score: *<130/80 mm Hg*
  - ✓ Older ambulatory, community-dwelling patients: *SBP <130 mm Hg*
  - ✓ Institutionalized older patients, those with high disease burden and comorbidities, or limited life-expectancy: *Consider a relaxed SBP goal of at least <150 mm Hg; <140 mm Hg in some patients if tolerated*
- ***Lifestyle Modification***
  - ✓ Implementation of lifestyle modifications successfully lowers BP often with results similar to those of therapy with a single antihypertensive agent. Combining multiple lifestyle modifications can have even greater BP lowering effects. Lifestyle modifications also have a favorable effect on other risk factors for cardiovascular events including dyslipidemia and insulin resistance, which are commonly encountered in the hypertensive population (Table 4.2)
- **Pharmacotherapy**
  - ✓ Several antihypertensive medications are available for the management of BP and should be used to combat the mechanism of HTN pathophysiology.
  - ✓ In the nonblack population (including patients with diabetes), initial treatment should include a thiazide type diuretic, calcium channel blocker, angiotension-converting enzyme inhibitor, or angiotension receptor blocker.

Table 4.2 Lifestyle modifications to prevent and manage hypertension[1]

Modification	Recommendation	SBP Reduction
Weight reduction	Maintain normal body weight (body mass index 18.5-24.9 kg/m^2)	5-20 mmHg/10 kg
Dietary modification	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8-14 mm Hg
Sodium reduction	Reduce dietary sodium intake to no more than 2.4-g sodium or 6-g sodium chloride	2-8 mm Hg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min/d, most days of the week)	4-9 mm Hg
Moderation of alcohol consumption	Limit consumption to no more than two drinks (eg, 700mL beer, 300 mL wine, or 90mL 80-proof whiskey) per day in most men, and to no more than one drink per day in women and lighter weight persons	2-4 mm Hg

- ✓ In the black population (including patients with diabetes), initial treatment should include a thiazide-type diuretic or calcium channel blocker. Patients with chronic kidney disease and older than 18 years, initial treatment should include an angiotension-converting enzyme inhibitor or angiotension receptor blocker. β-Blockers are generally no longer recommended as initial therapy except for patients with a compelling indication (eg, coronary artery disease or left ventricular dysfunction). Guidelines recommend combination therapy when the SBP is 20 mm Hg above goal or the DBP is 10 mm Hg above goal.

(1) Thiazide diuretics

- ✓ Hydrochlorothiazide: 12.5-50 mg PO once daily
- ✓ Indapamide: 1.25-2.5 mg PO once daily

- Thiazide diuretics are especially effective in the elderly and blacks where volume and heightened PVR are major contributors to elevated BP.
- In patients with renal insufficiency, thiazide diuretics are less effective. Thiazide diuretics become ineffective in the management of BP when creatinine clearance approaches 30 mL/min and below. At this point it becomes necessary to switch to (or add) a loop diuretic. Greater risk of developing DM than with ACEI, ARB, and CCB; use caution in patients at high risk of DM (e.g., family history, obesity)

---

[1] American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018

- **ADR:** glucose disturbance, electrolyte abnormality, goute
- **Monitor:** blood glucose, electrolyte, BUN/SCr, UA

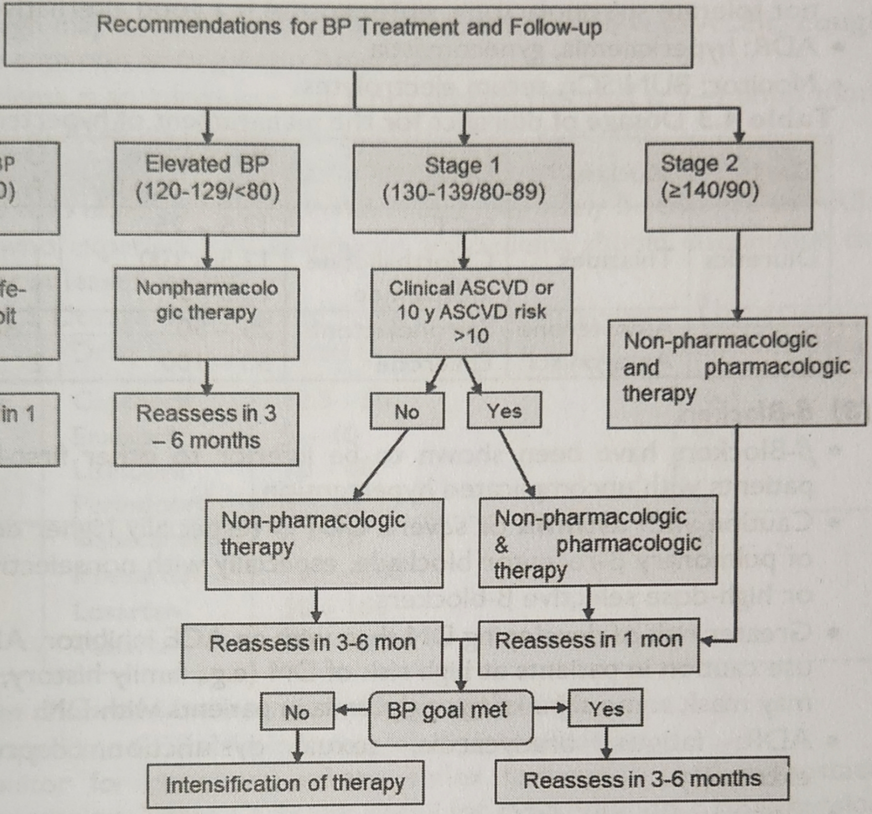

Recommendations for BP Treatment and Follow-up
Normal BP (<120/80)
Elevated BP (120-129/<80)
Stage 1 (130-139/80-89)
Stage 2 (≥140/90)
Optimal life-style habit
Nonpharmacologic therapy
Clinical ASCVD or 10 y ASCVD risk >10
Non-pharmacologic and pharmacologic therapy
Reassess in 1 year
Reassess in 3 – 6 months
No
Yes
Non-phamacologic therapy
Non-pharmacologic & pharmacologic therapy
Reassess in 3-6 mon
Reassess in 1 mon
No
BP goal met
Yes
Intensification of therapy
Reassess in 3-6 months

Figure 4.2 Recommendation for BP treatment[1]

(2) Aldosterone Antagonist

✓ Spironolactone: 25-50 mg PO once daily

- They can cause life-threatening hyperkalemia, especially when potassium is elevated at baseline, in patients with chronic kidney disease, or when concomitant medications predispose patients to hyperkalemia.
- Spironolactone is an effective and well-tolerated **add-on** therapy for appropriately selected patients. Because of its structural similarity to progesterone, dose-dependent antiandrogenic effects can occur. Responsible for gynecomastia and erectile dysfunction in men. It can cause breast pain or tenderness in both sexes, and can lead to menstrual irregularities in premenopausal women.

---

[1] MacLaughlin EJ, Saseen JJ. Hypertension. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Michael Posey LL. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e. McGraw Hill; 2023. Accessed January 29, 2023.

- **ADR:** glucose disturbance, electrolyte abnormality, goute
- **Monitor:** blood glucose, electrolyte, BUN/SCr, UA

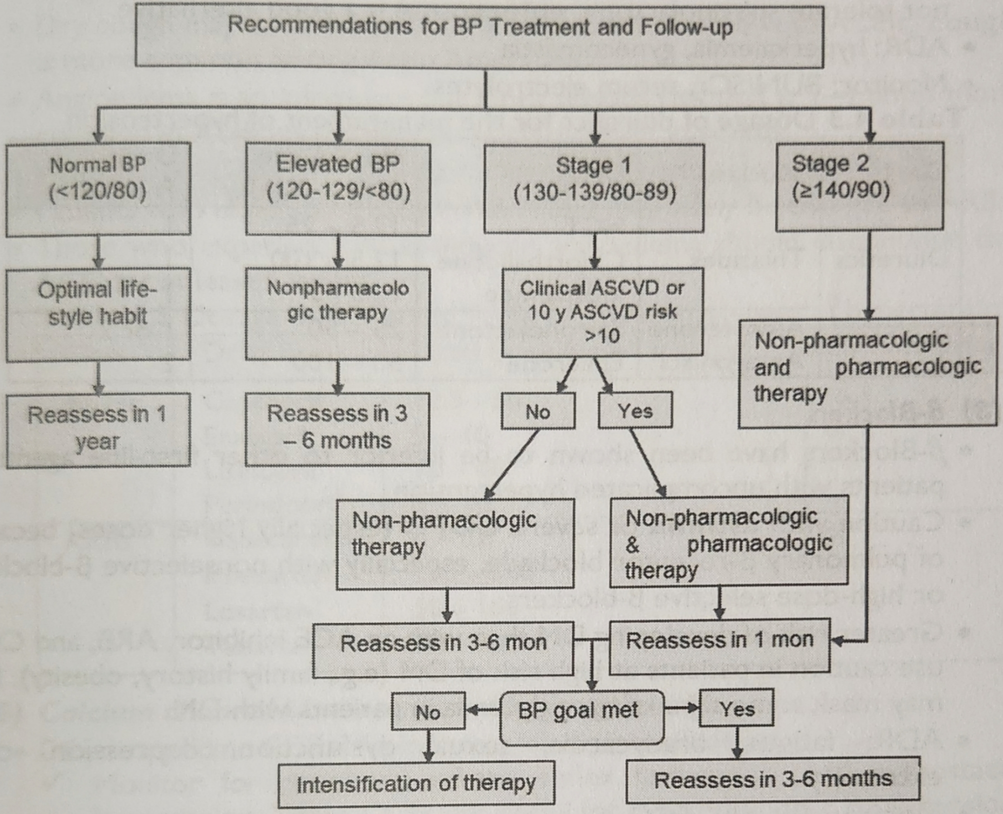

Recommendations for BP Treatment and Follow-up
Normal BP (<120/80)
Elevated BP (120-129/<80)
Stage 1 (130-139/80-89)
Stage 2 (≥140/90)
Optimal life-style habit
Nonpharmacologic therapy
Clinical ASCVD or 10 y ASCVD risk >10
Non-pharmacologic and pharmacologic therapy
Reassess in 1 year
Reassess in 3 – 6 months
No
Yes
Non-phamacologic therapy
Non-pharmacologic & pharmacologic therapy
Reassess in 3-6 mon
Reassess in 1 mon
No
BP goal met
Yes
Intensification of therapy
Reassess in 3-6 months

Figure 4.2 Recommendation for BP treatment[1]

(2) Aldosterone Antagonist

✓ Spironolactone: 25-50 mg PO once daily

- They can cause life-threatening hyperkalemia, especially when potassium is elevated at baseline, in patients with chronic kidney disease, or when concomitant medications predispose patients to hyperkalemia.
- Spironolactone is an effective and well-tolerated **add-on** therapy for appropriately selected patients. Because of its structural similarity to progesterone, dose-dependent antiandrogenic effects can occur. Responsible for gynecomastia and erectile dysfunction in men. It can cause breast pain or tenderness in both sexes, and can lead to menstrual irregularities in premenopausal women.

---

[1] MacLaughlin EJ, Saseen JJ. Hypertension. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Michael Posey LL. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e. McGraw Hill; 2023. Accessed January 29, 2023.

- Spironolactone is contraindicated in pregnancy because of the risk of feminizing male fetuses. For patients with resistant hypertension who do not tolerate spironolactone, **eplerenone** is a good alternative.
- ADR: hyperkalemia, gynecomastia
- Monitor: BUN/SCr, serum electrolytes

Table 4.3 Dosage of diuretics for the management of hypertension

Class	Subclass	Drug	Usual Dose Range, mg/day	Daily Frequency
Diuretics	Thiazides	HCT Chlorthalidone Indapamide	12.5 – 25 12.5 – 100 1.25 –5	1 1 1
	Aldosterone Antagonists	Spironolactone Epilerone	25 – 50 50 – 100	1 or 2 2

(3) β-Blockers

- β-Blockers have been shown to be inferior to other first-line agents in patients with uncomplicated hypertension
- Caution with **asthma** or severe **COPD** (especially higher doses) because of pulmonary β-receptor blockade, especially with nonselective β-blockers or high-dose selective β-blockers.
- Greater risk of developing DM than with an ACE inhibitor, ARB, and CCB; use caution in patients at high risk of DM (e.g., family history, obesity). BBs may mask some signs of hypoglycemia in patients with DM.
- ADR: fatigue, bradycardia, sexual dysfunction, depression, cold extremity
- Monitor: BP, HR, ECG

Table 4.4 Dosage of BBs for the management of hypertension

Class	Subclass	Drug	Usual Dose Range, mg/day	Daily Frequency
BBs	Cardioselective	Atenolol Metoprolol	25 - 100 50 – 100	1 1
	Non-selective Antagonists	Propranolol Timolol	160 – 480 50 – 100	2 1
	Mixed α - and β -blockers	Carvedilol Labetalol	12.5 – 50 200 - 800	1 2

(4) ACE Inhibitors and ARBs

- In patients with greater RAAS activation, initial therapy with an ACEI or ARB is logical including patients restricting salt intake, younger, white patients, and/or those with higher measured renin concentrations
- ACE inhibitors and ARBs are contraindicated in pregnancy, bilateral renal artery stenosis

- Monitor K closely, especially if renal impairment exists or another K-sparing drug or K supplement is used.
- Dry cough may occur in up to 20% of patients treated with ACEIs; **cough** is more common among Asian Americans.
- Angioedema is an infrequent but more serious risk that is 2–4 times more common in **African American patients** than in whites.
- Historically, ACEIs offered a significant cost advantage over ARBs
- Patients who experience cough with ACEIs may safely be changed to ARBs.
- Those who experience ACEI-induced angioedema should discontinue the ACEI for at least 6 weeks.

Table 4.5 Dosage of ACEis and ARBs for the management of hypertension

Class	Drug	Usual Dose Range, mg/day	Daily Frequency
ACEis	Captopril	12.5 - 50	2 to 3
	Enalapril	5 – 40	1 or 2
	Lisinopril	10 – 40	1
	Perindopril	4 – 16	1
ARBs	Cadesartan	8 – 32	1 or 2
	Irbesartan	150 – 300	1
	Losartan	50 – 100	1
	Valsartan	80 – 320	1

(5) *Calcium channel blockers: non-dihydropyridines*

- Dihydropyridine CCBs: Amlodipine, felodipine, nifedipine
  - ✓ Monitor for peripheral edema, reflex tachycardia, and orthostatic hypotension. These CCBs are useful for isolated systolic hypertension or use in African American patients
- Non-dihydropyridine CCBs: Diltiazem, verapamil
  - ✓ Indicated in hypertensive patients with comorbid conditions which would benefit from HR reduction (e.g. atrial fibrillation, stable angina)
  - ✓ Contraindicated in heart block and sick sinus syndrome
- ADR: Peripheral edema, headache, flushing
- Monitor: edema, BP

Table 4.6 Dosage of CCBs for the management of hypertension

Class	Subclass	Drug	Usual Dose Range, mg/day	Daily Frequency
CCBs	Dihydropyridines	Amlodipine	2.5 – 10	1 or 2
		Felodipine	5 – 10	1
		Nifedipine XL	30 – 90	1
	Non-dihydropyridines	Diltiazem LA	120 – 540	1
		Verapamil	100 - 400	1

(6) *Central α_2 agonists:* methyldopa: 250-1000 mg PO twice daily
- ADR: Bradycardi, dry mouth, orthostatic hypotension, rebound HTN
- Monitor: BP, HR

✍ **Compelling indications for the use of select antihypertensives**

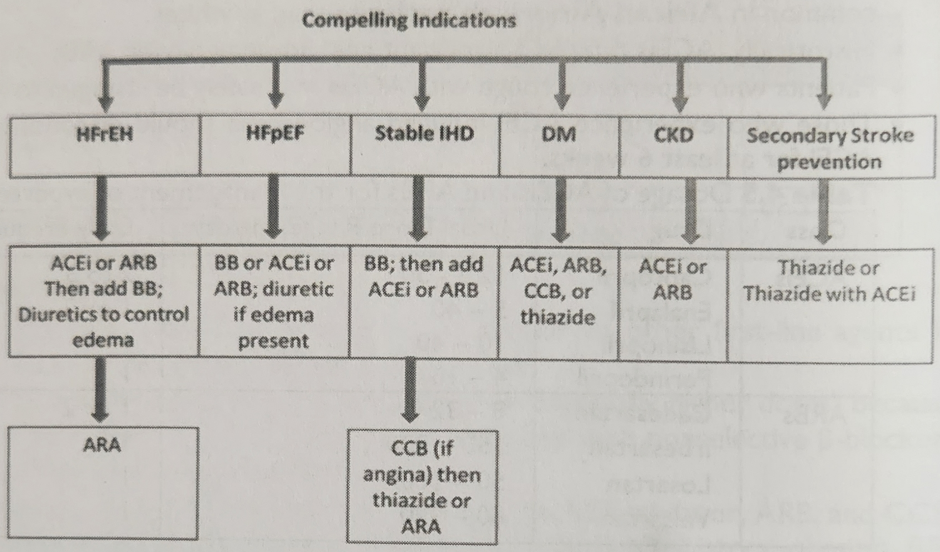

Compelling Indications
HFrEH
HFpEF
Stable IHD
DM
CKD
Secondary Stroke prevention
ACEi or ARB Then add BB; Diuretics to control edema
BB or ACEi or ARB; diuretic if edema present
BB; then add ACEi or ARB
ACEi, ARB, CCB, or thiazide
ACEi or ARB
Thiazide or Thiazide with ACEi
ARA
CCB (if angina) then thiazide or ARA

Figure 4.3: The most common compelling indications for individual drug classes

✍ **Combination therapy**

- A combination of two antihypertensive drugs is recommended for patients initially presenting with stage 2 hypertension. Using a fixed-dose combination product is an option for these types of patients and has been shown to improve adherence
- ASH recommendations for combination therapy

Preferred	**Acceptable**	**Less Effective**
ACEi/CCB	β-Blocker/thiazide	ACEi/β -blocker
ARB/CCB	CCB*/β -blocker	ARB/β -blocker
ACEi/thiazide	CCB/thiazide	CCB*/β -blocker
ARB/thiazide	Thiazide/potassium-sparing diuretic	Centrally acting agent/β -blocker

*dihydropyridine CCBs

✍ Follow-up and Monitoring

- After the initiation of antihypertensive therapy, patients should return for follow-up at monthly intervals until the BP goal is reached.
- More frequent visits are necessary for patients with stage 2 hypertension or complicating comorbid conditions or those with concerning laboratory levels that may be affected by therapy.
- Once BP goal is reached, follow-up visits can be at 3 to 6-month intervals.
- Serum creatinine and electrolytes should be monitored one to two times per year, perhaps more often in patients with chronic kidney disease.

✍ Special Populations

(1) Diabetes

- ✓ ACEIS or ARB are considered first line. The majority of patients with diabetes will need two or more medications to control their BP. The most rationale combinations include either an ACEI or ARB combined with a diuretic or CCB.

(2) Chronic Kidney Disease

- ✓ Treatment should consist of either an ACEI or ARB and diuretic in most patients. A loop diuretic should be substituted for a thiazide agent when GFR is markedly reduced (<30 mL/min/1.73 m^2).

(3) Heart Failure

- ✓ Hypertension doubles the risk of developing heart failure (HF) and 90% of patients with HF have a history of hypertension.
- ✓ ACEIs, ARBs, and BBs are the cornerstone of treatment.

(4) Ischemic Heart Disease

- ✓ The presence of hypertension increases the risk of coronary events and progression of atherosclerosis.
- ✓ In patients with angina, BBs should be used to lower heart rate and BP, alleviate angina symptoms, and improve survival.

(5) Cerebrovascular Disease

- ✓ The risk for ischemic stroke, hemorrhagic stroke, and dementia increases as a function of BP. BP control is the most important factor in the prevention of cerebrovascular disease.
- ✓ No specific agent or class of agents has been identified as the preferred method for BP control though preference should be given to diuretics, ACEIs, and ARBs.

(6) Resistant Hypertension

Key Concepts ***Resistant hypertension*** *is defined as failure to achieve BP goal with full doses of an appropriate three-drug regimen that includes a diuretic.*

- ✓ Causes of resistant hypertension include: volume overload, excess sodium intake, inadequate diuretic therapy, drug induced (non-adherence, inadequate dose, NSAIDs, illicit drugs, corticosteroids, oral contraceptives, erythropoietin), obesity, excessive alcohol intake.
- ✓ Management of patients with resistant hypertension include the addition of spironolactone, direct acting vasodilators, or referral to a specialist.

(7) Hypertensive Crises

- ✓ A ***hypertensive emergency*** is defined by a BP above 180/120 mm Hg with evidence of impending or progressive target organ dysfunction.
- ✓ These patients are susceptible to developing hypertensive encephalopathy, intracerebral hemorrhage, acute myocardial infarction, acute left ventricular failure with pulmonary edema, unstable angina pectoris, dissecting aortic aneurysm, or eclampsia.
- ✓ Immediate BP lowering is warranted but the extent and timing of BP lowering is not clearly defined.
- ✓ Patients are usually admitted for intensive care unit care and close follow-up. Intravenous medications used commonly.
  - ✓ ***Hydralazine*** (10 min onset, 1 – 4 hr duration): 5–10 mg by slow IV infusion every 4–6 hr
  - ✓ ***Enalaprilat*** (within 30 min onset, 12 – 24 hr duration):
  - ✓ ***Labetalol*** (5–10 min onset, 3–6 hr duration): 20–80 mg every 15 min or initial 0.3–1 mg/kg dose (max 20 mg) slow IV injection every 10 min or 0.4–1.0 mg/kg/hr infusion up to max 3 mg/kg/h
- ✓ When target organ damage is *absent* but BP is severely elevated, the event is deemed ***hypertensive urgency***.
- ✓ In hypertensive urgency, immediate BP lowering is less urgent and rapid-acting ***oral*** agents such as captopril, labetalol, or clonidine can be considered

(8) Women

- ✓ In women who are pregnant or are attempting to conceive, ACEIs and ARBs are contraindicated because of the risk of fetal developmental abnormalities.
- ✓ When drug therapy is warranted, methyldopa is the drug of choice
- ✓ BBs, especially labetalol, are considered alternatives to methyldopa.

4.2. Heart Failure

✍ **Definition**: HF is a complex clinical syndrome caused by any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood[1]. It is clinical state in which an abnormality of the heart is responsible for its inability to fill with or eject blood at a rate proportional to the requirements of the metabolizing tissues. HF is frequently, caused by a defect in myocardial contraction, and then the term myocardial failure is appropriate.

✍ **Formes of Heart Failure**

- **Low-output Vs High-output Heart Failure**
  - ✓ **Low-output HF:** occurs secondary to IHD, hypertension, dilated cardiomyopathy, and valvular and pericardial disease
  - ✓ **High-output HF:** occurs in patients with reduced systemic vascular resistance, i.e., hyperthyroidism, anemia, pregnancy, arteriovenous fistulas, beriberi, and Paget's disease
- **Acute Versus Chronic Heart Failure**
  - ✓ In **acute HF** the ***sudden*** reduction in cardiac output often results in systemic hypotension without peripheral edema.
  - ✓ **Chronic HF** is typically observed in patients with dilated cardiomyopathy or multivalvular heart disease and ***develops*** or ***progresses slowly***.
- **Right-sided Vs Left-sided Heart Failure**
  - ✓ **Left-sided HF:** in patients in whom the **left ventricle** is hemodynamically overloaded (e.g., aortic regurgitation) or weakened due to myocyte loss (e.g., post MI). it results in **dyspnea** and **orthopnea** as a result of pulmonary congestion
  - ✓ **Right-sided HF:** When the underlying abnormality affects the **right ventricle** primarily (e.g., primary pulmonary hypertension secondary to chronic pulmonary thromboembolism). Thes pateints develop edema, congestive hepatomegaly, and systemic venous distention.
- **Heart Failure with Reduced Ejection Fraction (HFrEF) or Systolic Dysfunction**
  - ✓ Defined as a clinical diagnosis of HF and an LVEF of 40% or less
  - ✓ Etiology
    - ↳ Two thirds of cases are attributable to ***coronary heart disease*** (CHD). One third of cases is attributable to nonischemic cardiomyopathy
      - ❖ Causes include: HTN, thyroid disease, obesity, stress, myocarditis, tachycardia, cardiotoxins: chemotherapeutic agents (anthracyclines, cyclophosphamide (high dose), 5-FU, trastuzumab/pertuzumab), alcohol, cocaine

---

[1] Parker RB, Rodgers JE. Chronic Heart Failure. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Michael Posey LL. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e. McGraw Hill; 2023. Accessed January 29, 2023.

- **Heart Failure with Preserved EF (HFpEF) or Diastolic Dysfunction**
  - ✓ Defined as an LVEF of 50% or greater; borderline HFpEF is LVEF 41%–49%. It accounts for about 30% of patients with HF.
  - ✓ Impaired ventricular relaxation and filling, normal wall motion
  - ✓ Most common cause is HTN (60%–89%)

✍ Causes of Heart Failure

- **Underlying causes**
  - ✓ Ischemic heart disease is responsible for about three-quarters of all cases.
  - ✓ Cardiomyopathies are second in frequency,
  - ✓ HTN remains an important cause
  - ✓ Congenital and valvular are less common causes.
- **Precipitating Causes**
  - ✓ **Infection:** The resulting fever, tachycardia, hypoxemia, and the increased metabolic demands may place a further burden on an overloaded, but compensated, myocardium of a patient with chronic heart disease.
  - ✓ **Arrhythmias**: **Tachy arrhythmias** reduce the time available for ventricular filling, contributing especially to diastolic HF; cause ischemic myocardial dysfunction in patients with IHD. **Slowing of the heart rate** associated with complete AV block or other severe bradyarrhythmias reduces cardiac output
  - ✓ **Physical, Dietary, Fluid, Environmental, and Emotional Excesses:** The sudden sodium intake as with a large holiday meal, the inappropriate d/c of drugs or other therapy for HF, blood transfusions, physical overexertion, excessive environmental heat or humidity, and emotional crises all may precipitate HF in patients who were previously compensated.
  - ✓ **Myocardial Infarction**: a new infarct may further impair ventricular function and precipitate HF
  - ✓ **Pulmonary Embolism:** Pulmonary emboli may result in further elevation of pulmonary arterial pressure, which in turn may produce or intensify ventricular failure
  - ✓ **Anemia**: In the presence of anemia, the oxygen needs of the metabolizing tissues can be met only by an increase in the cardiac output
  - ✓ However, a diseased, overloaded, but otherwise compensated heart may be unable to augment sufficiently the volume of blood that it delivers to the periphery.
  - ✓ **Thyrotoxicosis and Pregnancy**: Similar to anemia and fever, thyrotoxicosis and pregnancy are also high cardiac output states.

- ✓ The development or intensification of HF in a patient with previously compensated heart disease may actually be one of the first clinical manifestations of hyperthyroidism
- ✓ **Aggravation of Hypertension** is also a precipitating cause
- ✓ **Rheumatic, viral, and other forms of myocarditis**: Acute rheumatic fever and a variety of other inflammatory or infectious processes affecting the myocardium may precipitate HF in patients with or without preexisting heart disease
- ✓ **Infective Endocarditis:** The additional valvular damage, anemia, fever, and myocarditis that often occur as a consequence of infective endocarditis may, singly or in combination, precipitate HF

✍ **Pathophysiology**

- **Normal Cardiac Function**
  - ✓ Cardiac **output (CO)** is defined as the volume of blood ejected per unit time (L/min) and is the product of **heart rate** (HR) and **stroke volume** (SV):
    $CO = HR \times SV$
  - ✓ The relationship between CO and mean arterial pressure (MAP) is:
    $MAP = CO \times$ systemic vascular resistance (SVR)
  - ✓ **Heart rate** is controlled by the autonomic nervous system
  - ✓ **Stroke volume**, or the volume of blood ejected during systole, depends on **preload**, **afterload**, and **contractility. Left ventricular end-diastolic volume** is the primary determinant of **preload. Afterload** is the sum of forces preventing active forward ejection of blood by the ventricle. Inverse relationship exists between afterload (or SVR) and stroke volume such that *increasing afterload causes a decrease in stroke volume*. **Contractility** is the intrinsic property of cardiac muscle describing fiber shortening and tension development.
- Heart failure is a progressive disorder initiated by an event that impairs the ability of the heart to **contract** and/or **relax**. The **decrease in the heart's pumping capacity** results in the heart having to rely on **compensatory responses** to maintain an adequate cardiac output
- These **compensatory responses** include
  - ✓ Tachycardia and increased contractility through sympathetic nervous system (SNS) activation
  - ✓ An ↑in preload results in an increase in stroke volume
  - ✓ Vasoconstriction and
  - ✓ Ventricular hypertrophy and remodeling.

a) Increased preload (through Na+ and water retention)

- **Renal perfusion in heart failure is reduced** because of depressed cardiac output and redistribution of blood away from non vital organs. The kidney interprets the reduced perfusion as an ineffective blood volume, resulting in activation of the RAAS in an attempt to maintain blood pressure and increase renal sodium and water retention.

➔ RAAS activation *optimize stroke volume* but results in pulmonary and systemic congestion and edema formation and increased myocardial oxygen demand

b) Vasoconstriction and Increased Afterload

- To *redistribute blood flow away from nonessential organs to coronary and cerebral circulations* to support blood pressure, which may be reduced secondary to a decrease in cardiac output (mean arterial pressure = CO × SVR)
- A number of neurohormones contribute to the vasoconstriction including **NE, angiotensin II, endothelin-1**, *and* **arginine vasopressin** *(AVP)*

  ➔ this compensatory mechanism is to *maintain BP in face of reduced CO and shunts blood from nonessential organs to brain and heart; but it reuslts in* increased myocardial oxygen demand *and* increased afterload decreases stroke volume and further activates the compensatory responses

c) Tachycardia and increased contractility (due to SNS activation)

- The change in heart rate and contractility that rapidly occurs in response to a drop in cardiac output is primarily a result of release of NE from adrenergic nerve terminals,

  ➔ Sympathetic nervous system activation intends to maintain CO; but results in increased myocardial oxygen demand, shortened diastolic filling time and precipitation of ventricular arrhythmias

d) Ventricular hypertrophy and remodeling

- **Ventricular hypertrophy** is a term used to describe an *increase in ventricular muscle mass*. **Cardiac or ventricular remodeling** is a broader term describing changes in both *myocardial cells* and *extracellular matrix* that result in changes in the *size, shape, structure*, and *function* of the heart. *Angiotensin II, NE, endothelin, aldosterone, vasopressin* and *cytokines*, that are activated both systemically and locally in the heart play an important role in initiating the signal–transduction cascade responsible for ventricular remodeling. Pressure overload (and probably hormonal activation) associated with **hypertension** produces a **concentric hypertrophy** *(increase in the ventricular wall thickness without chamber enlargement)*. Conversely, **eccentric left ventricular hypertrophy** (myocyte lengthening with *increased chamber size* with minimal increase in wall thickness) characterizes the hypertrophy seen in patients with *systolic dysfunction or previous MI*

Remodeling process intended *to maintain CO and reduces myocardial wall stress; but* increases the risk of myocardial cell deat, diastolic and systolic dysfunction, *myo*cardial ischemia, arrhythmia and fibrosis

✍ **Symptoms**

- Respiratory symptoms: exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, night cough
- Other symptoms: fatigue, edema (from feet upwards), anorexia and weight loss, exercise intolerance
- Signs: Pulmonary rales, pleural effusion, neck vein distension and raised JVP, displaced apical impulse, gallop rhythm, tender hepatomegaly, cachexia and extremity edema

✍ **Investigations**

- CXR: Useful for detection of cardiac enlargement, pulmonary edema, and pleural effusions.
- ECG: To assess HR, rhythm, LVH, conduction, previous MI
- Echocardiography: ventricular performance, cardiac structure.
- Other tests: Blood chemistry, electrolytes, RFT, FPG, Lipid profile, CBC (Hgb/HCT, WBC), U/A

✍ **Management of Heart Failure**

- **Goals of therapy:** the goals of therapy in management of chronic heart failure are
  - ✓ To improve the patient's quality of life;
  - ✓ Relieve or reduce symptoms;
  - ✓ Prevent or minimize hospitalizations for exacerbations of heart failure;
  - ✓ Slow progression of the disease process; and
  - ✓ Prolong survival.

Management of HFrEF or systolic HF

- ***Non-pharmacologic therapy***
  - ➥ Prevent further cardiac injury: discontinue smoking, reduce weight if obese, control HTN, control DM, decrease alcohol intake
  - ➥ Restricting fluid and Na intake
  - ➥ Modest exercise
- **Pharmacologic therapy**

(1) Diuretics

Key Concepts *Diuretics are indicated in HF patients with evidence of fluid retention*

- Benefits
  - ➥ Short-term benefit (days): decreased jugular venous distension, pulmonary congestion, peripheral edema

  - Intermediate-term benefits (weeks to months): decreased daily symptoms, increased exercise tolerance
  - Long-term benefits (months to years): No benefit on mortality

Table 4.7 ACC/AHA Staging and NYHA Functional Classification[1]

Stage		Class	
A	At high risk of HF (uncontrolled risk factors) but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	Asymptomatic HF; no limitations in physical activity caused by HF symptoms
C	Structural heart disease with prior or current symptoms of HF	I	No limitations in physical activity caused by HFsymptoms
		II	Slight limitation of physical activity; asymptomatic at rest, but symptoms of HF with normal level of activity
		III	Marked limitations in physical activity because of HF symptoms; asymptomatic at rest
		IV	Symptoms of HF at rest or unable to carry out any physical activity
D	Refractory HF requiring specialized interventions	IV	Symptoms of HF at rest

- Dosing and administration considerations
  - Should be combined with an ACE inhibitor, β-blocker, and ARA
  - Start with a low initial dose and then double the dose and titrate according to the patient's weight and diuresis as needed
  - For a patient has fluid overload, initiate and adjust therapy to result in 0.5-1 kg of weight loss per day
  - Long-term therapy should be adjusted to maintain a euvolemic state
  - A loop diuretic can be combined with another diuretic class (e.g., thiazide diuretic) for synergy, if needed
  - Loop diuretics are preferred because of their greater diuretic capabilities; also retain efficacy with decreased renal function.
- Monitoring:
  - Monitor and replace K (goal with CVD is ≥4.0 mEq/L)

---

[1] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL: **2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.** *Journal of the American College of Cardiology* 2013, **62**(16):e147-e239.

  - Scr and renal function to avoid acute kidney injury with overdiuresis.

Table 4.8 Diuretics and recommended dosing for CHF

Agent	Oral BA (%)	Initial daily dose	Maximal daily dose (mg)	Duration of action (hr)
Loop diuretics (inhibit 20%–25% of sodium reabsorption)				
Furosemide	10–67	20–40 mg daily or BID	600	6–8
Bumetanide	80–100	0.5–1 mg daily or BID	10	4–6
Torsemide	80–100	10–20 mg daily	200	12–16
Ethacrynic acid	100	25–50 mg daily or BID	200	6–8

(2) ACE inhibitors

Key Concepts *ACE inhibitors are indicated in all patients with HFrEF and current or prior symptoms, unless contraindicated*

- Benefits:
  - **Decreased mortality** (25%–50% relative risk reduction compared with placebo depending on severity of HF)
  - **Decreased hospitalizations** (about 30% relative risk reduction compared with placebo)
  - Symptom improvement
  - Improved clinical status
  - Improved sense of well-being
- Dosing and administration considerations
  - Start low and double the dose every 1–4 weeks to target dose
  - Avoid use in patients who have experienced angioedema, pregnant or plan to become pregnant
  - Use caution if SBP is less than 80 mm Hg, SCr is greater than 3 mg/dL, K is greater than 5.0 mEq/L, or the patient has bilateral renal artery stenosis
- Monitoring
  - Monitor SCr and K for 1–2 weeks after initiating therapy or increasing the dose, especially in high-risk patients
  - Monitor BP and symptoms of hypotension (dizziness, lightheadedness)
  - Monitor angioedema (<1%): we can switch to angiotensin II receptor blockers (ARBs; cross-reactivity is 2.5%)
  - Monitor cough (20%): we can switch to ARBs (less than 1%)

Table 4.9 ACE inhibitors and recommended dose for CHF management

Agent	Starting dosage	Target dosage	Maximum dosage
Captopril	6.5 mg three times daily	50 mg three times daily	50 mg three times daily
Enalapril	2.5 mg twice daily	10 mg twice daily	20 mg twice daily
Lisinopril	2.5 – 5 mg daily	20 mg daily	40 mg daily
Perindopril	2 mg daily	8 mg daily	16 mg daily
Ramipril	1.5 – 2.5 mg daily	10 mg daily	10 mg daily

(3) Angiotensin receptor blockers

> **Key Concepts** *ARBs are recommended in patients with HFrEF with current or prior symptoms who are unable to take an ACE inhibitor due to cough and/or angioedema*

- Have not been proven superior to ACE inhibitors at target HF dosages.
- Benefits: decreased HF-related hospitalizations and decreased death from CV causes
- Dosing and administration
  - Start low and double the dose every 1–4 weeks to target dose
  - Avoid use in patients who have experienced angioedema, pregnant or plan to become pregnant
  - Use caution if SBP is less than 80 mm Hg, SCr is greater than 3 mg/dL, K is greater than 5.0 mEq/L, or the patient has bilateral renal artery stenosis
- Monitoring
  - Monitor SCr and K for 1–2 weeks after initiating therapy or increasing the dose, especially in high-risk patients
  - Monitor BP and symptoms of hypotension (dizziness, lightheadedness)

Table 4.10 ARBs and recommended dosing for CHF management

Agent	Starting dosage	Target dosage
Candesartan	4 – 8 mg daily	32 mg daily
Losartan	25 – 50 mg daily	150 mg daily
Valsartan	20 – 40 mg twice daily	16 mg twice daily

(4) β-Blockers

> **Key Concepts** *β-Blockers are recommended in all patients with HFrEF with current or prior symptoms unless contraindicated*

- Benefits (when added to an ACE inhibitors):
  - Decreased mortality (about 35% relative risk reduction compared with placebo)
  - Decreased hospitalizations (about 25% relative risk reduction compared with placebo)
  - Improvement in symptom and clinical status
- Dosing and administration considerations
  - Only **bisoprolol**, **carvedilol**, and **metoprolol succinate** are recommended in HFrEF.
  - Add to existing ACE inhibitor therapy (at least at a low dose) when HF symptoms are stable and patients are euvolemic.
  - Should **not** be prescribed without diuretics in patients with current or recent history of fluid retention
  - Start low and increase (double) the dose every 2 weeks (or slower, if needed) to target dose.
  - Aim to achieve target dose in 8–12 weeks
  - Avoid abrupt discontinuation; can precipitate clinical deterioration
  - Should be considered even in patients with reactive airway disease or asymptomatic bradycardia
- Monitoring
  - BP, HR, and symptoms of hypotension or bradycardia (monitor in 1–2 weeks). Thes symptoms occur in about 1% of patients when the β-blocker is titrated slowly. If these symptoms appear, lower the dose by 50%
  - Increased edema or fluid retention (monitor in 1–2 weeks): 1% to 2% more common than with placebo. Edema responds to diuretic increase
  - Fatigue or weakness: 1% to 2% more common than with placebo. It usually resolves spontaneously in several weeks. It may require dosage decrease or discontinuation

Table 4.11 β-Blockers and recommended dosing for CHF management

Agent	Starting dosage	Target dosage
Bisoprolol	1.25 mg daily	10 mg daily
Carvedolol	3.125 twice mg daily	25 mg twice daily
Carvedolo CR	10 mg daily	80 mg daily
Metoprolol Succinate	12.5 – 25 mg daily	200 mg daily

(5) Aldosterone Receptor Antagonist

Key Concepts *ARAs are recommended in patients with NYHA class II–IV with an LVEF of 35% or less to reduce morbidity and mortality unless a contraindication exists. Patients with NYHA class II should have a history of CV hospitalization or elevated brain natriuretic peptide (BNP) levels. Recommended to reduce morbidity and mortality in patients after an MI when they have an LVEF <40% with symptoms of HF or an LVEF <40% and DM*

- Benefits of spironolactone in NYHA class III and IV HF
  - Decreased mortality (30% relative risk reduction compared with placebo)
  - Decreased hospitalizations for HF (35% relative risk reduction compared with placebo)
  - Improved symptoms
- Benefits of eplerenone in NYHA class II HF
  - Decreased composite endpoint of death from CV causes or hospitalization from HF (37% relative risk reduction compared with placebo)
  - Decreased death from CV causes (24% relative risk reduction compared with placebo)
  - Decreased hospitalizations for HF (42% relative risk reduction compared with placebo)
  - Decreased mortality (24% relative risk reduction compared with placebo)
- Benefits of eplerenone in left ventricular dysfunction after MI
  - Decreased mortality (15% relative risk reduction compared with placebo)
  - Decreased composite endpoint of death from CV causes or hospitalization for CV events (13% relative reduction compared with placebo)
- Dosing and administration considerations
  - Should be added to ACE inhibitor (or ARB) and β-blocker therapy
  - SCr should be less than 2.5 mg/dL for men and less than 2.0 mg/dL in women (or eGFR >30 mL/minute/1.73 m2), and K should be less than or equal to 5.0 mEq/L.
  - In the absence of hypokalemia (K less than 4.0 mEq/L), supplemental K is not recommended when taking an ARA

- Monitoring
  - K and SCr within 2–3 days, again at 7 days after starting therapy, monthly for first 3 months, and every 3 months thereafter. If the dose of ACE inhibitor or ARB is increased, restart monitoring.
  - Hyperkalemia: bout 20% of patients. Decrease dose by 50% or discontinue if K is greater than 5.5 mEq/L
  - Gynecomastia: Spironolactone, reported at a rate of 10% in clinical trials. Eplerenone can be considered as an alternative to spironolactone if gynecomastia is present.

Table 4.12 ARAs and recommended dosing for CHF management

Parameters	Epeleronone	Spironolactone
eGFR ≥ 50 mL/min/1.73 m^2 and K ≤ 5 mEq/L	25 mg daily	12.5 - 25 mg daily
Maintenance dose after 1 mo if K ≤ 5 mEq/L and eGFR ≥ 50 mL/min/1.73 m^2	50 mg daily	25 mg daily or twice daily
eGFR 30–49 mL/min/1.73 m^2 and K ≤ 5 mEq/L	25 mg every other day	12.5 mg daily or every other day
Maintenance dose after 1 mo if K ≤ 5 mEq/L and eGFR 30–49 mL/min/1.73 m^2	25 mg daily	12.5 - 25200 mg daily

(6) Sodium-Glucose Cotransporter Type 2 (SGLT2) Inhibitors

- Initially developed for diabetes given their glucose-lowering potential by blocking renal tubular glucose reabsorption, SGLT2 inhibitors are also benefical in HF. These agents *inhibit glucose and sodium reabsorption in the proximal renal tubule* which promotes urinary glucose excretion and causes a modest diuresis
- Treatment with SGLT2 inhibitors leads to osmotic diuresis and natriuresis, reduction in arterial pressure and stiffness, and a shift to ketone-based myocardial metabolism. Additional benefit may be related to the reduction of preload and afterload, thereby reducing cardiac stress and injury and ultimately leading to reduced myocardial hypertrophy, fibrosis, and remodeling.
- In patients with HFrEF and NYHA class II-IV symptoms, both ***dapagliflozin*** and ***empagliflozin*** *reduced the risk of worsening HF and cardiovascular death* compared to placebo. Importantly, these benefits were observed both in patients with and without diabetes. Similarly, ***empagliflozin*** (fixed dose of 10 mg daily) also reduced the primary outcome of cardiovascular death or HF hospitalization in patients with HFpEF.

(7) Digoxin

> **Key Concepts** *Digoxin can be beneficial in decreasing hospitalizations in patients with HFrEF; should be added after ACE inhibitor (or ARB) and β-blocker therapy*

- Benefits: improved symptoms, improved exercise tolerance, decreased hospitalizations (28% relative risk reduction compared with placebo), **no effect on mortality**
- Dosing and administration considerations
  - For most patients, 0.125 mg/day is adequate to achieve the desired serum concentration. Consider dosing 0.125 mg every other day in patients older than 70 years, those with impaired renal function, or those with low lean body mass.
  - No indication to load patients with digoxin in the setting of HF
  - Avoid abrupt discontinuation; can precipitate clinical deterioration
- **Monitoring**
  - Serum concentrations should be less than 1 ng/mL; in general, concentrations of 0.5–0.9ng/mL are suggested. This minimizes the risk of adverse effects and ventricular arrhythmias associated with increased concentrations.
  - Risk of toxicity increases with age and renal impairment. Risk of toxicity increases also in the presence of hypokalemia, hypomagnesemia, or hypercalcemia.
  - Signs of toxicity generally include nausea, vomiting, vision changes
  - SCr should be monitored because the drug is primarily cleared renally

(8) Hydralazine/isosorbide dinitrate

> **Key Concepts** ***Hydralazine/isosorbide dinitrate*** *is recommended in addition to ACE inhibitors and β-blockers to reduce morbidity and mortality for patients self-described as African American with NYHA class III or IV HFrEF. May be useful in patients with current or prior symptoms of HFrEF who are unable to tolerate an ACE inhibitor or an ARB.*

- Benefits
  - Decreased mortality (43% relative risk reduction compared with placebo in African American patients)
  - Reduced pulmonary congestion and improved exercise tolerance
- Dosing and administration considerations
  - Hydralazine 75 to 300 mg daily in 3 or 4 divided doses; isosorbide dinitrate 60–120 mg daily in 3 or 4 divided doses. Fixed-dose BiDil

(hydralazine 37.5 mg plus isosorbide dinitrate 20 mg) with a goal dose of 2 tablets three times daily

- Monitoring
    - Headache
    - Hypotension
    - Drug-induced lupus (with hydralazine)

(9) Sacubitril/valsartan

> **Key Concepts** ***Sacubitril/valsartan*** *is an alternative to ACE inhibitors or ARBs. Replacement of ACE inhibitors or ARBs by sacubitril/valsartan is recommended to further reduce morbidity and mortality.*

- Benefits
    - Decreased composite endpoint of death from CV causes or hospitalization for HF (20% relative risk reduction compared with enalapril monotherapy)
    - Decreased all-cause mortality (16% relative risk reduction) and CV death (20% relative risk reduction) compared with enalapril monotherapy
    - Decreased hospitalization for HF (21% relative risk reduction compared with enalapril monotherapy)
- **Dosing and administration considerations**
- Initial dose: for those who are not currently taking ACE inhibitor or ARB, or switching from low doses of ACE inhibitor or ARB: sacubitril 24 mg/valsartan 26 mg twice daily. For those switching from an ACE inhibitor or ARB at a standard dosage: sacubitril 49 mg/ valsartan 51 mg twice daily
- Maintenance dose: Double the dose every 2–4 weeks to a target dose of sacubitril 97 mg/ valsartan 103 mg twice daily, as tolerated. If switching from an ACE inhibitor, allow a 36-hour washout period before initiating sacubitril/valsartan
- Monitoring
    - Observe for signs and symptoms of angioedema and hypotension.
    - Monitor renal function and K 1–2 weeks after initiating therapy or increasing the dose, especially in high-risk patients (e.g., preexisting hypotension, DM, K supplements, azotemia)

(9) Other medication therapies

- **Anticoagulation**: recommended for HF with permanent, persistent, or paroxysmal AF. This is not recommended in the absence of AF, prior stroke, or a cardioembolic source
- **Antiarrhythmics**: given the neutral effects on mortality, the preferred antiarrhythmics in patients with HFrEF are dofetilide (AF/atrial flutter) and amiodarone.

- **Algorithm for the Management HFrEF**

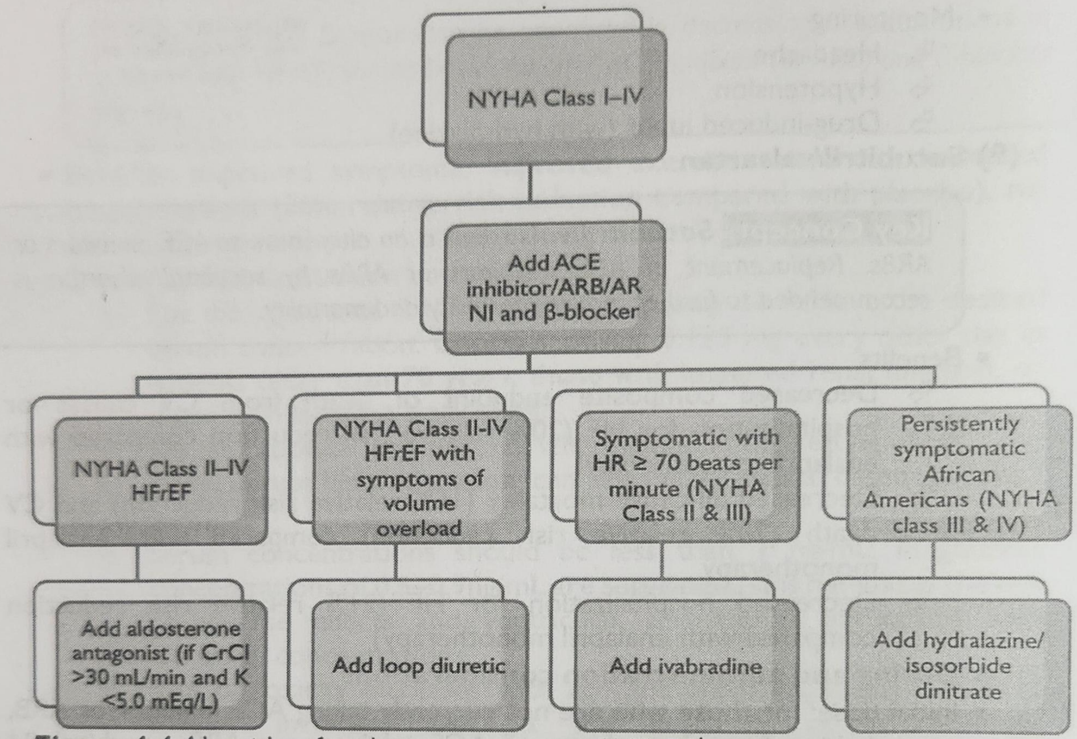

NYHA Class I–IV
Add ACE inhibitor/ARB/ARNI and β-blocker
NYHA Class II–IV HFrEF
NYHA Class II-IV HFrEF with symptoms of volume overload
Symptomatic with HR ≥ 70 beats per minute (NYHA Class II & III)
Persistently symptomatic African Americans (NYHA class III & IV)
Add aldosterone antagonist (if CrCl >30 mL/min and K <5.0 mEq/L)
Add loop diuretic
Add ivabradine
Add hydralazine/ isosorbide dinitrate

Figure 4.4 Algorithm for the management of HFrEF[1]

✍ Acute and Advanced Heart Failure

- Patients with AHF present with symptoms of worsening fluid retention or decreasing exercise tolerance and fatigue. Patients can be described as "**wet**" or "**dry**" depending on volume status. "Wet": patients with volume/fluid overload (eg, edema and jugular venous distension [JVD]). "Dry" refers to euvolemic patients. And "**warm**" or "**cool**" based on adequacy of tissue perfusion. "Warm": patients with adequate CO to perfuse peripheral tissues (and hence the skin will be warm to touch), "cool" refers to patients with evidence of hypoperfusion (skin cool to touch with diminished pulses).
- Invasive hemodynamic monitoring with invasive IV lines (e.g., Swan-Ganz pulmonary artery catheters) to provide objective data for assessing:

---

[1] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL: **2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines**. *Journal of the American College of Cardiology* 2013, **62**(16):e147-e239.